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The Lack of Effect of Methimazole Therapy in Lepromatous Leprosy

Reassessment by Examination of Bacterial Morphology[1]

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Following O'Byrne's report ([10]) of the efficacy of antithyroid drugs in leprosy, an examination of the mechanism of action of methimazole in lepromatous leprosy was undertaken. In a preliminary report of this study ([9]), a lack of correspondence was noted between the clinical appearance of the patients and the histopathologic appearance of serial skin biopsies obtained during methimazole therapy. Recent reports that the morphologic appearance of *Mycobacterium leprae* bears a close relationship to the ability of these organisms to multiply in the mouse foot pad ([11]), and that changes in the morphology of the bacilli occur with regularity during original treatment with dapsone ([12]), suggested that a retrospective assessment of methimazole therapy in our patients with lepromatous leprosy might now be possible. The suggestions of other workers ([2, 3, 6]) that methimazole therapy of lepromatous leprosy is ineffective have been confirmed.

METHODS

The method employed for measurement of the morphologic index (MI, the per cent of bacilli that are uniformly and brightly stained) in acid-fast-stained sections of skin biopsy specimens, has been described in detail and its validity demonstrated ([8]). In brief, the morphology of 300 bacilli was examined in a paraffin section of each skin biopsy specimen stained by the Fite-Faraco ([4]) method. Available for review were sections of 53 skin biopsy specimens obtained from 13 patients with lepromatous leprosy during the trial of methimazole therapy that had been carried out in 1961 and 1962. Skin biopsies were made before the institution of methimazole therapy, and at intervals during the period of methimazole administration ranging in duration from three to 14 months, during which time no other chemotherapeutic agent was administered. A detailed description of the methimazole trial has been published ([9]), and a study of the response of thyroid function has also appeared ([7]).

RESULTS

The course of the MI's measured from sections of the skin biopsy specimens obtained during methimazole therapy is summarized in Figure 1. Of the nine patients with an initial MI greater than 0, this index remained unchanged or increased in eight, despite periods of therapy sufficiently long so that an effective drug might have been expected to produce a decrease of the MI ([12]). In addition, there was an increase of the MI of two of the four patients who began methimazole therapy with an MI of

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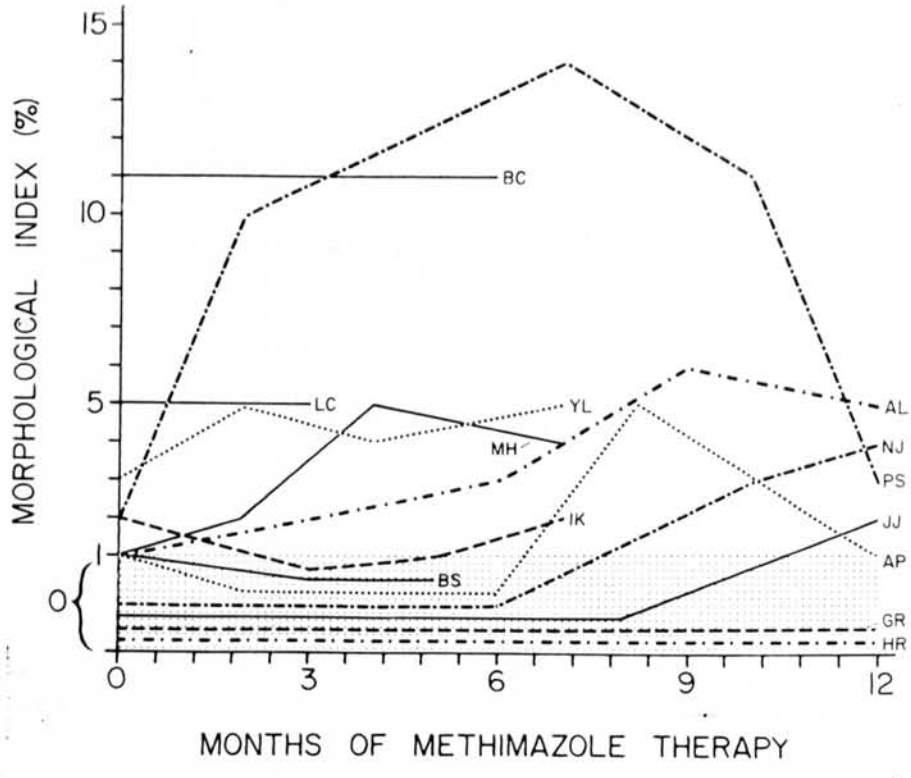

FIG. 1. Course of the morphologic index (MI) in 13 patients with lepromatous leprosy during a trial of methimazole therapy.

0. Thus, in 10 of these 13 patients, there was a failure of response and even deterioration during methimazole therapy, demonstrated by the criterion of the MI measured from tissue sections.

The course of the MI, similarly measured, of two patients treated originally with dapsone is presented in Figure 2 (Patients CB and RK). Also presented in this figure is the course of the MI in a patient (SA) suspected of harboring dapsone-resistant *M. leprae* during retreatment with dapsone in doses of 50 mgm. daily. The rather prompt fall of the MI's of the two original-treatment patients to levels not significantly different from 0 stands in sharp contrast to the behavior of the MI during methimazole therapy. The failure of the MI of patient SA to change, despite seven months of dapsone in therapeutic dosage, is similar to the behavior of the MI during methimazole therapy.

DISCUSSION

In the study of the mechanism of action of methimazole in lepromatous leprosy, changes in thyroid function were observed by means of repeated thyroid function tests. Hypothyroidism and thyroid enlargement occurred regularly in these patients. We thought, naively, that the response of lepromatous leprosy to methimazole therapy could be evaluated easily by means of repeated clinical examinations and photographs and histopathologic examination of serial skin biopsies. Although a number of patients seemed to improve clinically, grave difficulties were encountered in assessment of the response of the lepromatous process to methimazole therapy. The availability of a new criterion of response of leprosy to a drug, i.e., the change in the MI, seemed to offer an opportunity to evaluate the results of this earlier study more critically.

Once we were satisfied that bacterial morphology in tissue sections was comparable to that in smears of tissue homogenates, the application of the technic of measurement of the MI to sections of serial skin biopsies taken from patients during methimazole administration seemed to be justified. The MI's obtained failed to demonstrate the decrease expected during effective chemotherapy that has been described in serial skin scrapings of patients to whom therapeutic doses of dapsone were being administered ([12]), and which may be seen to have occurred in the two original-treatment patients presented here. Indeed, some of the patients treated with methimazole seem, by the morphologic criterion, to have "relapsed" during methimazole therapy.

That the changes (or lack of change) of the MI's during methimazole therapy are not merely random may be seen by contrast to the course of the two original-treatment patients during dapsone therapy. Additional evidence that the failure of the MI's to decrease during methimazole therapy, is meaningful is found by examination of the courses of these patients subsequent to the termination of the methimazole trial. Patients LC and BC, who were placed on treatment with a sulfone and isoniazid, each suffered the first of a series of severe bouts of erythema nodosum leprosum (ENL) six to nine months after the maximal dose of sulfone had been achieved. Biopsies at this time revealed MI's of 0, and yielded no growth in the mouse foot pad. A biopsy specimen obtained from NJ, after only intermittent therapy for two years, revealed an MI of 2 per cent and yielded growth in the foot pad. Biopsies performed on MH, IK, YL, JJ and PS one to 15 months following the initiation of dapsone in therapeutic dosage, have revealed an MI of 0. AL, after two and two and one-half years of dapsone in full dosage, had biopsies yielding MI's of 2 per cent respectively. AL, as well as SA, has had many previous courses of substituted sulfones, especially sodium glucosulfone (Promin), in the past, and is suspected of harboring dapsone-resistant organisms. Some of these changes of the MI are indeed quite small. It is important, in this connection, to note that the precision of this method of measurement of the MI has been shown ([8]) to be such that an estimate of 2 per cent is significantly different from 0 or 4 per cent at the 95 per cent level of confidence.

It is of interest to consider what it was

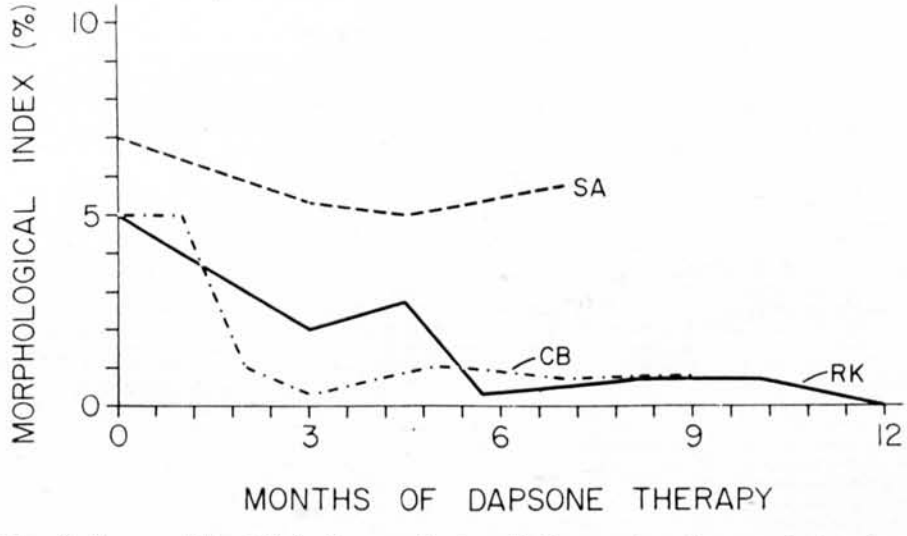

FIG. 2. Course of the MI in three patients with lepromatous leprosy during dapsone administration. For greater ease of presentation, the ordinate has been lengthened between 0 and 1 per cent. All points that fall within the stippled area between 0 and 1 per cent have values of 0.

that led us to believe that the patients improved during methimazole therapy. In retrospect, it appears that we misinterpreted the significance of ENL. Six patients, viz., MH, NJ, JJ, AP, AL and PS, had had severe ENL prior to methimazole therapy. During the trial of methimazole, ENL was either not evident or was very mild for seven to 12 months. Davison [3] reported that patients treated with a combination of dapsone and methimazole had less ENL than patients treated with dapsone alone. The work of several groups of investigators [1, 5, 12] may be interpreted as showing that ENL is a mark of effective treatment. If the patients who demonstrated no response to methimazole had had no ENL throughout the period of methimazole therapy, this would have been consistent with this formulation of ENL. In the six patients who experienced improvement of ENL during methimazole therapy, however, ENL recurred, in a few cases explosively, after months of treatment, while methimazole was being continued. In five of these six patients, the MI was at or near its peak value at the time ENL recurred. It would seem, therefore, that some additional mechanism of ENL must be invoked to explain this phenomenon in the patients treated with methimazole.

It seems important to consider the reasons for a reassessment of the efficacy of a drug that has already been "demonstrated" to be without effect in lepromatous leprosy. This study of methimazole was completed prior to the appearance of two of the three articles reporting unfavorable experiences with this drug. Latapí and Beirana [6], describing the results of a three-month course of methimazole therapy in 10 patients with leprosy, stated that they recognized neither clinical nor bacteriologic improvement in these patients. They emphasized, on the other hand, the side effects of this treatment, which included goiter formation, exacerbation of ENL, and, in three patients, an unspecified illness so severe as to require blood transfusion.

Browne and Hogerzeil [2] treated five patients with small doses of methimazole (15 mgm. daily) for nine months. Side effects, consisting mainly of rather nonspecific complaints, were of such importance that no patient was able to take the drug without interruption. Two patients were reported to have improved clinically during the trial, while two were unimproved and one became much worse. The two patients manifesting clinical improvement also showed marked improvement of the bacterial index, while the remaining three demonstrated no change. One of the two showing clinical improvement and a decrease of the bacterial index, had no change of the MI, while, in the other, the MI decreased from 35 per cent to 0 after 10 months of treatment. One of the remaining patients, whose clinical assessment showed no change and whose bacterial index was unchanged after 10 months of methimazole therapy, demonstrated a similar decrease of the MI. These authors concluded that methimazole therapy was without benefit in lepromatous leprosy and recommended that larger scale trials of this drug not be carried out.

Davison [3] compared methimazole in a dosage of 40 mgm. daily for one year with dapsone alone, and with dapsone plus methimazole, each regime being administered to a group of 20 patients with lepromatous leprosy. Each group showed some improvement clinically as well as by a fall of the bacterial index. By these criteria, however, methimazole was not as effective as dapsone, and did not add to the efficacy of dapsone when the two drugs were administered together.

Thus, although the reports of three investigations attest to a lack of efficacy of methimazole, only one [2] employed the MI in the assessment of the response to therapy, and in this study, an insufficient dose of the drug was given, as indicated by the failure of hypothyroidism and thyroid enlargement to appear. Waters and Rees [12] have demonstrated the unsuitability of the bacterial index, employed in one of the studies [3] to demonstrate the ineffectiveness of therapy, as a criterion of the response of lepromatous leprosy to therapy. The present study, the first to apply the criterion of the MI in a trial of methimazole administered in dosage sufficient to interfere with thyroid function, demonstrates clearly the lack of therapeutic effect during this trial.

SUMMARY

Study of the morphology of *M. leprae* in acid-fast-stained sections of skin biopsy specimens obtained during the course of a trial of methimazole therapy in 13 patients with active lepromatous leprosy, has demonstrated the utility of this laboratory technic, and has confirmed previous impressions that the treatment of leprosy with methimazole is equivalent to nontreatment. No evidence has been found that hypothyroidism is beneficial to patients with lepromatous leprosy.

RESUMEN

Estudio de la morfología del *M. leprae* en secciones teñidas con características acidoresistentes en muestras de biopsias obtenidas durante el curso de un ensayo de tratamiento con methimazol en 13 pacientes con lepra lepromatosa activa, ha demostrado la utilidad de esta técnica de laboratorio, y ha confirmado impresiones previas que el tratamiento de la lepra con methimazol es equivalente a no hacer tratamiento. No se ha encontrado prueba que el hypothyroidismo es benéfico para los pacientes con lepra lepromatosa.

RÉSUMÉ

On a étudié la morphologie de *M. leprae* dans des coupes d'échantillons de biopsies cutanées colorées pour la recherche des acido-résistants. Ces échantillons avaient été obtenus au cours d'un essai thérapeutique du méthimazole mené chez 13 malades atteints de lépre lépromateuse active. Cette étude a démontré l'utilité de cette technique de laboratoire; elle a aussi confirmé les impressions antérieures qui suggéraient que la traitement de la lèpre par le méthimazole est équivalent à l'absence de traitement. Aucune observation n'a été faite permettant de croire que l'hypothyroidisme présenterait un quelconque avantage pour les malades atteints de lèpre lépromateuse.

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